Office of Environmental Health Hazard Assessment

Joan E. Denton, Ph.D., Director
Headquarters • 1001 I Street • Sacramento, California 95814
Mailing Address: P.O. Box 4010 • Sacramento, California 95812-4010
Oakland Office • Mailing Address: 1515 Clay Street, 16th Floor • Oakland, California 94612

Linda S. Adams
Secretary for Environmental Protection

Arnold Schwarzenegger
Governor

MEMORANDUM

TO: Gerald W. Bowes, Ph.D., Manager
Toxicology and Peer Review Section
State Water Resources Control Board
1001 I Street, 15th Floor
Sacramento, CA 95814

FROM: David M. Siegel, Ph.D., Chief,
Integrated Risk Assessment Branch
1001 I Street, 12th Floor
Sacramento, CA 95814

DATE: August 17, 2007

SUBJECT: REQUEST FOR EXTERNAL PEER REVIEW OF A PROPOSED HUMAN REFERENCE DOSE (RfD) FOR METHAMPHETAMINE

This memorandum is my request for you to initiate the process to obtain reviewers through the University of California to provide external peer review of a methamphetamine RfD* developed by the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) staff. The present request is only for the review of the proposed methamphetamine RfD. An exposure assessment and calculation of a surface reference exposure level (REL) are being developed, and will be subject to external peer review in a separate report.

Under the provisions of Health and Safety Code Section 25354.5, OEHHA, in cooperation with the Cal/EPA Department of Toxic Substances Control (DTSC), is required to prepare documentation supporting a risk-based exposure standard (i.e., a "cleanup level") for methamphetamine residues on surfaces to ensure protection of the health of all persons who subsequently occupy a residence that had a former clandestine methamphetamine laboratory. The

*RfDs are doses (expressed in units of mg/kg-day) at or below which adverse health effects are not likely to occur. A central assumption is that a threshold exists below which adverse effects will not occur in a population; however, such a threshold is not observable and can only be estimated. An RfD is a quantitative estimate of the lowest dose at which a toxic effect will occur, combined with uncertainty factors that account for variability in sensitivity in the human population and uncertainty in the toxicity database. The RfD for methamphetamine will be combined later with estimates of exposure to methamphetamine residues on surfaces to generate an REL.

cleanup standard will be developed by DTSC and based on the REL. To ensure that the cleanup standard for methamphetamine is health protective, both the human reference dose and the exposure assessment from which REL is developed, must be scientifically defensible.

We anticipate having a draft document describing development of a methamphetamine RfD available for external peer review by early October 2007. We request that the review be completed within 30 days upon receipt of the report. Public review of the document will be scheduled for the beginning of January with the incorporation of the external reviewers' comments.

We believe that the desirable areas of expertise for peer reviewers of this assessment should be the following, in order of importance:

1. Human Risk Assessment: dose-response assessment
2. Neuropharmacology: drugs of abuse
3. Clinical research

There are three attachments to this memorandum. Attachment I summarizes development of the proposed RfD. Attachment II identifies the scientific issues to be reviewed by external the peer-reviewers. Attachment III lists the individuals involved in the development of (1) the RfD; and (2) the exposure assessment and REL (in progress).

If you have any questions, please contact me at 916-322-5624 or at, dsiegel@oehha.ca.gov. The staff contact for this proposal is Dr. Charles Salocks, who can be reached at 916-323-2605 or at, csalocks@oehha.ca.gov. Thank you for your consideration of this request.

Attachments (3)

cc: George V. Alexeeff, Ph.D.
Deputy Director for Scientific Affairs

Charles Salocks, Ph.D.
Integrated Risk Assessment Branch

John Ferderer
Contracts & Business Services Branch

Cory Yep
Office of Legislation and Regulatory Policy
Department of Toxic Substances Control
1001 I Street
PO Box 806
Sacramento, California 95812-0806

Attachment I: Summary of the development of a sub-chronic human reference dose (RfD) for methamphetamine

I. Background

The clandestine synthesis of methamphetamine is a growing public health and environmental concern. It is estimated that for every pound of methamphetamine synthesized there are six or more pounds of hazardous materials or chemicals produced. In addition to concerns over the health and well being of peace officers and public health officials, there is increasing concern about potential health impacts on the public and unknowing inhabitants, including children and the elderly, who subsequently occupy dwellings where illegal drug labs have been located. To address these health concerns, the provisions of Health and Safety Code Section 25354.5 require that the Office of Environmental Health Hazard Assessment (OEHHA) develop a risk-based assessment for methamphetamine that DTSC could use to set a cleanup standard to ensure protection of the health of all persons who subsequently occupy a former clandestine methamphetamine lab.

II. Rationale

The processes that are used to develop an RfD for methamphetamine and an REL for surface methamphetamine residues are based on principles of human health risk assessment. Essentially, these principles require that the toxicity of a chemical and the magnitude of exposure to it be individually characterized in order to estimate its potential health risk. Documentation of OEHHA's evaluation of the toxicity of methamphetamine, which presents the basis for the RfD, is provided in this report. An analysis of potential exposure to methamphetamine residues in an indoor environment, which provides the basis for the REL, is provided in a separate report that will be submitted for review at a later date. The risk assessment procedures and assumptions that OEHHA adopted to assess the toxicity of methamphetamine and indoor exposure to surface residues are consistent with those used and developed by OEHHA and U.S. EPA for establishing risk-based cleanup levels for other contaminants.

III. Development of RfD

The report describes the toxicity of methamphetamine and provides justification for a sub-chronic RfD for the drug. RfDs are doses at or below which adverse health effects are not likely to occur. A central assumption is that a threshold exists below which adverse effects will not occur in a population over an exposure duration of several months[1]; however, such a threshold is not observable and can only be estimated. Areas of uncertainty in estimating effects among a diverse human population are addressed using extrapolation and uncertainty factors. To develop

[1] OEHHA anticipates a post-cleanup exposure scenario in which the duration of exposure does not exceed 4-6 months. Therefore, a sub-chronic reference dose will be used to establish the risk-based cleanup level.

an RfD for methamphetamine, the critical effect(s) of the drug must be identified, based on a thorough review of the relevant pharmacological and toxicological literature. According to U.S.EPA, a *critical effect* is the first adverse effect, or its known precursor, that occurs to the most sensitive species as the dose rate of an agent increases. Therefore, if an exposure standard (i.e., a cleanup level) for a chemical is set low enough to prevent the occurrence of its critical effect, then the standard will prevent the occurrence of any other toxic effect as well. For methamphetamine, we have taken a health-protective position that *any* effect induced by the drug is an adverse effect and potentially, a critical effect.

The literature review for methamphetamine was limited almost exclusively to research reports describing methamphetamine's effects in humans under controlled conditions. Due to the wealth of published studies in human subjects and the substantial differences in the pharmacokinetics and pharmacodynamics of methamphetamine in laboratory animals and humans, studies of the effects of methamphetamine in laboratory animals were not generally consulted for this report.

In the calculation of an RfD, *uncertainty factors* are used to account for data gaps, uncertainties and variability in the published toxicological literature. Uncertainty factors usually have a numerical value of 10 or 3, and function to reduce the experimentally determined "no observed adverse effect level" (NOAEL) or "lowest observed adverse effect level" (LOAEL). Since the critical effect for methamphetamine was based on a 16-week clinical study that identified a human LOAEL, standard 10-fold uncertainty factors were used to account for inter-individual variability in the human population and extrapolation from a LOAEL to a NOAEL. An additional 3-fold uncertainty factor was adopted to account for uncertainties in the completeness of the toxicity database.

Attachment II: Description of Scientific Issues to be Addressed by Peer Reviewers

The statute mandate for external scientific peer review (Health and Safety Code section 57004) states that the reviewer's responsibility is to determine whether the scientific portion of the proposed rule is based upon sound scientific knowledge, judgment, methods and practices. We request that each reviewer's responsibility is to make this determination for each of the following issues that constitute the scientific basis of the proposed methodology. An explanatory statement is provided for each issue to focus the review. For those work products which are not proposed rules, as is the case here, reviewers must measure the quality of the product with respect to the same exacting standard as if it was subject to Health and Safety Code Section 57004.

While developing the methamphetamine sub-chronic toxicity criterion staff identified a number of key issues in the analysis. These are issues on which staff would especially like to have review and receive comments.

1. **Determination of appropriateness of the primary study as a basis for estimation of a sub-chronic RfD for methamphetamine.** There is a large volume of literature on the effects of methamphetamine on humans. The study chosen to base the REL on was a multi-dose, 16–week, weight control study using pregnant females. The primary concern leading up to this analysis was the assumed sensitivity of children to methamphetamine contamination. Justification was given to support the study chosen.
2. **Appropriateness of the statistical analysis of the data from the primary study.** The author of the primary study did not perform any statistical analysis of the data. However, the paper provided the raw data and an analysis was conducted by OEHHA staff using these data.
3. **Adequacy and relevance of the supplementary documentation to support the primary study.** There are many different effects caused by methamphetamine exposure that have been studied in people. A number of these are discussed using relevant citations, but not all articles or effects have been included.
4. **Consistency of the supplementary documentation with the primary study.** While not all effects and articles on the effect of methamphetamine were included, there was an attempt to use the same level of detail describing the effects discussed.
5. **Adequacy of justification for the selected uncertainty factors.** There is always uncertainty involved in estimating an RfD for any compound. Using the commonly practiced method, uncertainty factors were chosen for developing the methamphetamine sub-chronic RfD. Each uncertainty factor was discussed in detail.

Reviewers are not limited to addressing only the specific issues presented above, and are asked to contemplate the broader perspective.

(a) In reading the proposed analysis and human reference dose development, are there any additional scientific issues that are part of the scientific basis of the proposed human reference dose not described above?

(b) Taken as a whole, is the human reference dose based upon sound scientific knowledge, methods, and practices?

The preceding guidance is to ensure that reviewers have an opportunity to comment on all aspects of the scientific basis of the proposed human reference dose. At the same time, reviewers also should recognize that the OEHHA has a legal obligation to consider and respond to all feedback on the scientific portions of the proposed human reference dose. Because of this obligation, reviewers are encouraged to focus feedback on the scientific issues that are relevant to the central elements being proposed.

Attachment III: Individuals involved in the development of the (1) proposed methamphetamine RfD; and (2) exposure assessment and REL.

There were no individuals involved in or consulted with during the development of the RfD outside of State service.

OEHHA and DTSC staff are working with the individuals identified below, under contract, to develop the follow-up exposure assessment and REL for methamphetamine. The product of that work will be submitted for external peer review at a later date.

1. Xiaoying Hui, M.S., M.D.
   Department of Dermatology
   University of California San Francisco

2. Howard I. Maibach, M.D.
   Department of Dermatology
   University of California San Francisco